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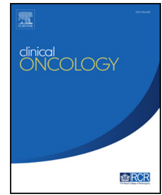

Overview

Where Do We Look for Markers of Radiotherapy Fraction Size Sensitivity?

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Abstract

The response of human normal tissues to radiotherapy fraction size is often described in terms of cellular recovery, but the causal links between cellular and tissue responses to ionising radiation are not necessarily straightforward. This article reviews the evidence for a cellular basis to clinical fractionation sensitivity in normal tissues and discusses the significance of a long-established inverse association between fractionation sensitivity and proliferative indices. Molecular mechanisms of fractionation sensitivity involving DNA damage repair and cell cycle control are proposed that will probably require modification before being applicable to human cancer. The article concludes by discussing the kind of correlative research needed to test for and validate predictive biomarkers of tumour fractionation sensitivity.
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Key words: Cancer; DNA repair; fractionation; hypofractionation; normal tissues; radiotherapy

Statement of Search Strategies Used and Sources of Information

The search strategy included PubMed index terms ionising radiation, radiosensitivity, hypofractionation, normal tissues, tumours.

Introduction

The responses of normal tissues to radiotherapy fraction size have long been assumed to have a basis in cellular recovery, one of the 4 Rs of classical radiobiology [1]. This article reviews the evidence for a cellular basis to fractionation sensitivity and discusses the significance of the close association between fractionation sensitivity and proliferative indices. A molecular model of normal tissue fractionation sensitivity involving DNA repair and cell cycle control is proposed that needs to incorporate genetic and epigenetic modifications before being applicable to cancer. The article concludes by considering how clinicians might investigate the applications of predictive biomarkers of tumour fractionation sensitivity.

Target Theory and the Cellular Basis of Fractionation Sensitivity

The first application of target theory in radiation biology proposed the nucleus as the subcellular target of ionising radiation [2]. In the current article, the cell is considered as the critical target underpinning tissue responses to fraction size (fractionation sensitivity). Oncologists are often introduced to fractionation sensitivity via the linear quadratic equation, an empirical model describing the non-linear relationship between fraction size and tissue response. The relationship is described by the α/β ratio, values $\geq$10 Gy being typical of early-reacting normal tissues and lower values reflecting the greater sensitivity to fraction size of late-reacting normal tissues (see Figure 1) [3–5]. The same model is used to describe the non-linearity or

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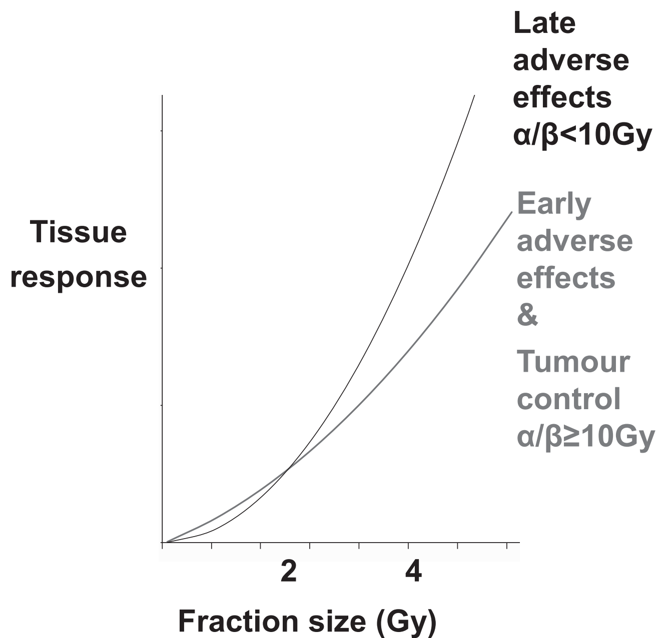

Fig 1. Schema illustrating the traditional model of fractionation sensitivity in normal and malignant tissues, late-reacting normal tissues being more sensitive to fraction size than early-reacting normal tissues and most cancers.

'bendiness' of the *in vitro* clonogenic cell survival curve; an important question to ask is to what extent does the fractionation sensitivity of tissues reflect this cellular response [4,6]. The molecular correlates of cellular recovery focus on DNA double-strand break (DSB) induction and repair, so an even more fundamental question is whether and to what extent does DNA repair explain the fractionation sensitivity of normal tissues.

A central role of DNA damage repair as a determinant of radiation response is shown by the exquisite tissue sensitivity to ionising radiation of rare patients with ataxia telangiectasia, but an association between *in vitro* cellular radiosensitivity and normal tissue response is difficult to detect in non-syndromic patients [7,8]. Among a long list of reasons for past failed attempts to correlate *in vitro* cellular responses to clinical responses in non-syndromic individuals is that *in vitro* assays cannot take into account modifying interactions between different target cell populations and between cells and extracellular matrix [9–11]. This limitation is also relevant to testing the relationship between classical cellular recovery and tissue fractionation sensitivity. If the fractionation sensitivities of all normal tissue target cell populations could be reliably measured *in vivo*, the estimates of α/β for each target cell type contributing to the function of a particular tissue would incorporate the modifying effects of cell–cell and cell–matrix interactions. The challenge would then be to build a biological model describing how the responses of individual target cell populations explain the fractionation sensitivity of the tissue or organ as a whole.

Human skin is a good place to start thinking about this, as responses to radiotherapy are well characterised. For example, the fractionation sensitivity of desquamation can be considered in relation to a single population of target stem cells in the basal epidermis [12]. The low sensitivity of moist desquamation to fraction size (high α/β value) has been accurately quantified for treatment times >10 days, and there is a very close association between desquamation and depletion of basal epidermal cells [13,14]. Human skin biopsies collected during and after 40 Gy in 10 fractions over 5 weeks compared with 50 Gy in 25 fractions over 5 weeks generate values of $\alpha/\beta \geq 10$ Gy for basal cell depletion, consistent with a causal link between basal cell depletion and fractionation sensitivity of desquamation [14]. Acute epidermal responses are probably influenced by interactions with the underlying dermis, which two-dimensional keratinocyte cultures cannot take into account. The capillary dilatation responsible for erythema is clearly a dermal response, sharing the same high α/β value as desquamation [13]. The impossibility of dissociating desquamation from erythema is consistent with a direct relationship between them. The vasodilator vascular endothelial growth factor (VEGF), over-expressed by basal epidermis in some chronic inflammatory diseases and induced by radiation, is one of several paracrine mechanisms that might be responsible [15,16]. If moist desquamation is severe, permanent epidermal stem cell depletion causes healing by secondary intention (granulation) where skin atrophy, fibrosis and telangiectasia are classified as 'consequential' effects characterised by high α/β values [17]. If moist desquamation heals without scarring, late onset skin atrophy, fibrosis and telangiectasia are regarded as 'true' late effects, each having low α/β values. The relevant target cells for telangiectasia include endothelial and myoendothelial cells. Endothelium is also a likely target cell to consider in relation to atrophy, where the latter may be partly a response to tissue ischaemia and hypoxia.

If there are no fibroblasts, there can obviously be no fibrosis [18]. If confluent fibroblast monolayers are irradiated, they enter a prolonged G1 cell cycle arrest and upregulate collagen production rather than undergo apoptosis or suffer mitotic catastrophe [19–21]. High levels of stable chromosomal translocations in fibroblasts cultured from human skin irradiated many years previously suggest that fibrosis can be, at least in part, the product of surviving, irradiated fibroblasts rather than immigrant cells [22]. However, the fractionation sensitivity of fibrosis probably needs to consider more than resident fibroblasts. In systemic sclerosis, dermal fibrosis represents a response to microvascular occlusion (endothelial target cell) and hypoxia [23,24]. Platinum electrodes confirmed cutaneous hypoxia many years after high dose radiotherapy for head and neck cancer, so perhaps a target theory applied to fibrosis needs to consider endothelial cells. Endothelial cells and fibroblasts are not the only putative target stem cells when considering the fractionation sensitivity of fibrosis. Smooth muscle cells differentiate into collagen-producing fibroblasts in several human fibrotic states, including atherosclerosis [25]. Fibroblast progenitors might also be unexposed, immigrant cells, such as marrow-derived fibrocytes [26]. When describing fibrogenic responses to fraction size, a target cell model assumes that the intracellular target is DNA and the relevant

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